Attorney's Docket No.: 07898-038001 / PH-425PCT-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Shimon Sakaguchi
Serial No. : 09/284,114
Filed : April 7, 1999
Title : A MOUSE STRAIN WITH NATURAL ONSET OF AUTOIMMUNE ARTHRITIS

Art Unit : 1633
Examiner : Janet M. Kerr, Ph.D.

Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

1. I, Shimon Sakaguchi, Ph.D., having an address at Higashi-hiraki-cho 20, Takano, Sakyo-ku, Kyoto 606-8107, Japan, am the sole inventor of the above-referenced United States patent application serial no. 09/284,114. I am a professor of Experimental Pathology at the Institute for Frontier Medical Sciences, Kyoto University, and am an expert in the general fields of experimental pathology and immunology, particularly, in the field of arthritis. I was considered an expert in these fields in 1996 at the time of the invention.

2. I have read the specification and the file history, including past and the outstanding office actions, and Applicant's responses, for the above-identified patent application. I understand the issues presented by the Patent Office in the Office Action mailed August 1, 2000, regarding the pending claims of the application (referred to hereinafter as "the invention").

3. It is my understanding that one of the Patent Office's concerns is that the claimed inbred mouse, designated SKG, was not sufficiently altered by the hand of man and, therefore, is not statutory subject matter.

4. However, without the inventive identification of the mutation, and without the "hand of man," or selective breeding and further characterization, the claimed inbred strain could not have been developed. It is my belief that without the conceptual input (the discovery and recognition of the new strain) and considerable amount of labor (the inbreeding, isolation, testing, further inbreeding and further testing to confirm the presence of a new inbred strain) by

me the mutation giving rise to the SKG phenotype would have been lost and never would have been "made" or "manufactured" into the new and useful product of the claimed invention.

5. To further set forth and emphasize the great amount of labor involved in developing the new claimed inbred strain, the following is a description of the breeding and selection process used in obtaining the SKG mouse.

6. The Balb/c mouse colony from which the SKG mouse was obtained after a year of breeding in my lab did not, to the best of my knowledge, contain any animal exhibiting the characteristics of the claimed SKG mouse. I knew that the Balb/c strain, when compared with other strains, is genetically more susceptible to autoimmune diseases upon manipulation of the immune system, although the strain does not spontaneously develop autoimmune disease (see, e.g., Sakaguchi, S., and Sakaguchi, N, "Thymus and Autoimmunity: Capacity of the normal thymus to produce pathogenic self-reactive T cells and conditions required for their induction of autoimmune disease," J. Exp. Med. 172:537-545, 1990). The autoimmune diseases to which the Balb/c strain had been reported to be genetically susceptible included arthritis (see, Sakaguchi (1990) supra). I therefore intentionally used the Balb/c strain for maintaining a closed colony for detection of any immunologically altered mice as a result of naturally occurring alterations in their genome. I carefully inspected the mice for any visually discernable abnormalities, such as paralysis of extremities and joint swelling, because I was interested in immunologically mediated neurological or musculoskeletal diseases; furthermore, I had experience in detecting joint swelling, as described in my publication Sakaguchi (1990) supra. Specialized expertise is required to detect joint swelling in mice.

7. The Balb/c mouse colony from which the SKG strain originated was maintained for nearly one and a half years before a female mouse with joint swelling was found by the inventor. In this mouse colony, usually one to two males and four females were kept in a cage; and five such cages for breeding were maintained to produce Balb/c mice. When female mice became pregnant in these cages, they were separated to a single cage until they gave birth

and then weaned the offspring. Next, breeding pairs (two males and four females) were prepared from these offspring. Because the Balb/c mice thus produced were used for immunological experiments, their health status was occasionally checked by visual inspection, serological check of autoantibodies, and radiographic and histological examination. The inventor selected this particular breeding strategy to make it possible to detect recessive mutations if the phenotype of the mutation can be detected. When the joint-swollen female mouse was detected, it was isolated. This initial "SKG" female mouse with joint swelling was subsequently bred with another apparently normal male mouse in the colony. Their offspring developed similar joint swelling; thus, the genetic inheritance of the joint swelling phenotype was first considered to be autosomal dominant because this first set of offspring developed joint swelling. It turned out later that the male mouse itself bore the mutation, i.e., the mutation was already shared by other mice in the same colony. Although the incidence of arthritis in these offspring was first estimated to be about 33% when assessed at three months, it was determined that at the third generation, when the offspring from joint-swollen female and male mice were kept observed until 6 months of age, all of them developed arthritis. This difference was mainly because I first did not notice swelling of small finger joints and only counted advanced arthritis in large joints. From the third generation to the present generation (now maintained at more than 5 generations), the phenotype of the SKG strain has been stable in terms of the incidence and the severity of the arthritis.

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8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully Submitted

Date: January 31, 2007

Shimon Sakaguchi, Ph.D.

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